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(19)

(54) NEW PROCESS FOR THE MANUFACTURE OF NUCLEOSIDES

(71) We, SCHERING AKTIENGESELLSCHAFT, a Body Corporate organised according to the laws of Germany, of Berlin and Bergkamen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with a new process for the manufacture of nucleosides.

Processes for the manufacture of nucleosides are known. Thus, for example, from Y. Furukawa et al (Chem. Pharm. Bull. *16*, 1067/1968/) it is known that purines react with 1-O-acyl- or 1-O-alkyl-derivative of a sugar in the presence of a Friedel-Crafts catalyst to form the corresponding N-glycosides, and in German Patent DBP No. 1,919,307 there is described a process for the manufacture of nucleosides, characterized in that silylated N-heterocycles are reacted with protected 1-halo-, 1-O-alkyl- and especially 1-acyl-sugars in the presence of Friedel-Crafts catalysts.

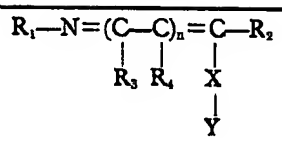
The industrial use of the known processes has been especially disadvantageous, because the separation of the salts of Lewis acids or Friedel-Crafts catalysts formed during the reaction often gives difficulties in working up the reaction mixture, and additional chemical operations are necessary. In particular these disadvantages also cause a reduction in the yield of the desired end product.

It has now been found that the Friedel-Crafts catalysts, for example $SnCl_4$, can be replaced as catalysts by known trialkylsilyl esters, preferably trimethylsilyl esters of mineral acids, for example perchloric acid or sulphuric acid, or of strong organic acids, for example trifluoromethane sulphonic acid.

The present invention accordingly provides a process for the manufacture of a nucleoside, wherein a sugar derivative that contains an -O-acyl or -O-alkyl group or a halogen atom in the 1-position and may contain at least one protected hydroxyl group in another position is reacted with a silylated organic base, preferably a silylated heterocyclic organic base, in the presence of an ester selected from trialkylsilyl esters, preferably trimethylsilyl esters, of mineral acids and trialkylsilyl esters, preferably trimethylsilyl esters, of strong organic acids and, if desired, any protected hydroxyl group in the resulting nucleoside is converted into a free hydroxyl group.

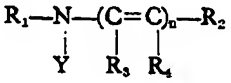
Particularly preferred as trialkyl silyl esters are all easily accessible mono-, di- or poly-trimethylsilyl esters, for example trimethylsilyl perchlorate $[(CH_3)_3Si—OClO_3]$ and the trimethylsilyl esters of trifluoracetic acid and trifluoromethane sulphonic acid $[(CH_3)_3Si—OCOCF_3$ and $(CH_3)_3SiO—SO_2CF_3$, respectively]. By the replacement of, for example, $SnCl_4$ by the trimethylsilyl esters of mineral acids the harmful formation of emulsions and colloids during working up is avoided and the yields are increased.

In accordance with the process of the present invention all the silylated organic bases that are known generally to those skilled in the art can be used. There are suitable, for example, organic bases of the general formula



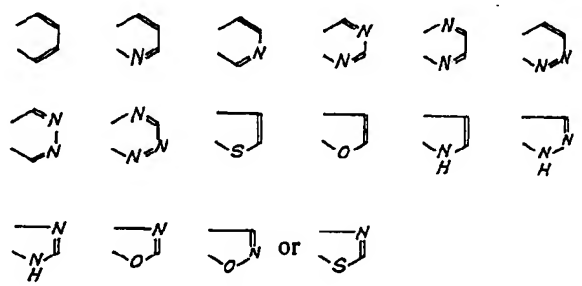
(Ia)

or



(Ib)

in which X represents an oxygen or sulphur atom, n represents 0 or 1, R_1 and R_2 each represents an unsubstituted or substituted organic hydrocarbon group (which may be saturated or unsaturated) or together represent a divalent organic group (which may contain one or two nitrogen atoms), R_3 and R_4 each represents a hydrogen atom or an alkyl, alkoxycarbonyl or alkylaminocarbonyl group or together represent either a divalent group of the formula



or a corresponding divalent group that is substituted (for example as indicated in the next but one paragraph), and Y represents a trialkyl silyl group, especially a trimethylsilyl group.

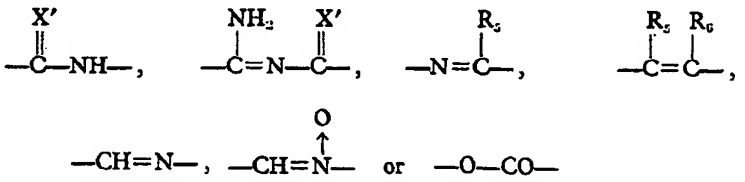
When R_1 and R_2 represent any desired separate organic groups, they represent more especially alkyl groups containing 1 to 10 carbon atoms, preferably containing 1 to 4 carbon atoms, or aryl or aralkyl groups. There may be mentioned, for example, methyl, ethyl, propyl and butyl groups.

The divalent groups represented by R_1 and R_2 together and also by R_3 and R_4 together may contain, for example, one or more of the following substituents, namely alkyl groups containing 1 to 10 carbon atoms, trifluoromethyl, acyl, hydroxyl, alkoxy, acyloxy, carboxyl, carboxamido, alkoxycarbonyl, dialkylaminocarbonyl, amino and nitro groups, oxo groups (attached to carbon or nitrogen atoms) and halogen atoms.

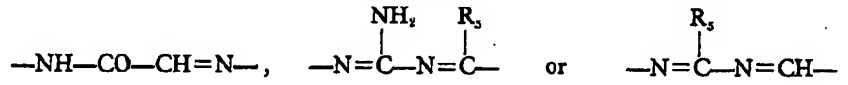
Preferred starting bases are silylated organic bases in which R_1 and R_2 in the above formulae are connected together in a ring and especially in such a manner that the heterocyclic base contains five or six atoms in the ring, of which one to three are nitrogen atoms.

The silylated organic bases having the formulae Ia and Ib are thus preferably derived from the following heterocyclic bases, namely uracil, cytosine, 6-azauracil, 2-thio-6-azauracil, thymine, an N-acyladenine, guanine, lumazine, imidazole, pyrazine, thiazole and triazole, which may be substituted by one or more of the above mentioned substituents listed for the divalent groups represented by R_1 and R_2 together and also R_3 and R_4 together.

For the case in which R_1 and R_2 are connected together in a ring, the divalent group represented by R_1 and R_2 together is more especially a

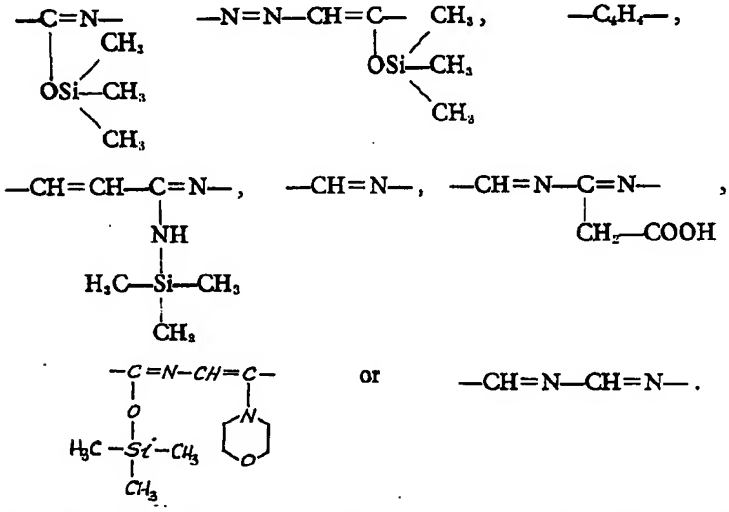


group, when $n=1$, and a



group, when $n=0$, in which X' represents an oxygen or sulphur atom and R_5 and R_6 each represents a hydrogen atom or an alkyl, alkoxycarbonyl or alkylaminocarbonyl group.

The divalent group represented by R_1 and R_2 together may also advantageously be a group of the formula



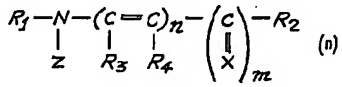
The sugar derivatives used in the process of the present invention are preferably derived from ribose, desoxyribose, arabinose and glucose.

Advantageously, all the free hydroxyl groups of the sugar are protected. As sugar protecting groups there are suitable the protecting groups customarily used in sugar chemistry, for example acyl groups, for example benzoyl, para-chlorobenzoyl, para-nitrobenzoyl and para toluyl groups, and benzyl groups.

In the nucleosides obtained in accordance with the process of the present invention the free or protected sugar group is preferably connected to the nitrogen atom in a β-glycoside manner.

When in accordance with the process of the present invention there are to be made nucleosides which contain O-acyl-protected sugar groups, there come into consideration in addition to the protecting groups already mentioned also, *inter alia*, the groups of the following acids, namely propionic acid, butyric acid, valeric acid, caproic acid, oenanthic acid, undecanoic acid, oleic acid, pivalic acid, cyclopentylpropionic acid, phenylacetic acid and adamantane carboxylic acid.

The process of the present invention can be used in general for the preparation of nucleosides. Preferred products of the process are nucleosides of the general formula II



in which R_1, R_2, R_3, R_4, X and n have the meanings given above, Z represents a free or protected sugar group, and m represents 0 or 1. The nucleosides that can be prepared in accordance with the process and especially the products of the general formula II, are biologically active. By virtue of their specific solubility they can be administered, depending on the choice of the substituents, either systemically as aqueous or alcoholic solutions, or locally as salves or jellies.

The nucleosides, depending on the starting compounds used, have, for example, an enzyme-inhibiting, antibacterial, antiviral, cytostatic, antisporiatic or inflammation-inhibiting action.

The reaction of the silylated organic base, for example a base of the general formula Ia or Ib, with 1-O-acyl-, 1-O-alkyl- or 1-halogeno-derivative of a free or

protected sugar in the presence of a catalyst in accordance with the process of the present invention is carried out in a suitable solvent, for example in methylene chloride (CH_2Cl_2), 1,2-dichloroethane ($ClCH_2CH_2Cl$), chloroform, benzene, toluene, acetonitrile, ethylene chloride, dioxan, tetrahydrofuran, dimethylformamide, carbon disulphide, chlorobenzene, sulpholan or molten dimethyl sulphone.

The reaction may be carried out at room temperature or at a higher or lower temperature, but preferably at a temperature within the range of from 0 to 100°C. The reactants are generally used in the reaction in approximately equimolar quantities; however, a silylated heterocycle is often used in a small excess, in order to obtain a conversion of the sugar component that is as far as possible quantitative. Often 0.1 equivalent of the catalyst suffices, for each equivalent of the sugar component.

The catalysts used for the new process, as compared with the formerly used Lewis acids or Friedel-Crafts catalysts, have the great advantage that they can be immediately and quantitatively removed by simple agitation with a bicarbonate solution without the formation of emulsions or colloids, because they are immediately hydrolysed to a salt and hexamethyl-disiloxane (boiling point 98°C), which is removed during the withdrawal of the solvent.

The catalyst can be prepared in accordance with the literature, for example, from $AgClO_4$ with $(CH_3)_3SiCl$ which gives $(CH_3)_3Si—OClO_3$ together with AgCl [U. Wannagat and W. Liehr, Angew. Chemie *69*, 783 (1957)], or, as in the case of the trimethylsilyl ester of trifluoromethane sulphonic acid, easily from CF_3SO_3H and $(CH_3)_3SiCl$ [H. C. Marsmann and H. G. Horn, Z. Naturforschung *B 27*, 4448 (1972)] with the use of a neutral solvent, for example benzene, or without a solvent. Filtration of any salts formed with the exclusion of moisture leads to stable solutions of the silyl esters used as catalysts.

From acylated 1-O-alkyl- and 1-O-acyl-sugars and the catalyst there are formed in the reaction in the process of the present invention a sugar cation contained in, for example, a mineral acid salt and also a silylated O-alkyl- or O-acyl-derivative. The sugar salt then reacts with, for example, a silylated pyrimidine with the formation of a nucleoside and the renewed formation of the silylester of the mineral acid, so that catalytic quantities of the silyl ester of the mineral acid suffice.

The yields obtained in the process of the present invention are higher than those of the aforesaid known processes. Moreover, there are formed preponderantly β-derivatives of the sugars and the undesired α-anomers are formed only in minor quantities or not at all.

For the preparation of nucleoside containing free hydroxyl groups, the hydroxyl-protecting groups can be removed in the usual manner, for example, by alcoholic solutions of ammonia or alcoholates, aqueous or alcoholic alkali and also, in the case of the benzyl ethers, by reduction or hydrogenation.

The following Examples illustrate the invention:—

Example 1

To 5.15 mmoles of 2,4-bis-(trimethylsilyloxy)-pyrimidine and 5 mmoles of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in 20 ml of 1,2-dichlorethane were added 2.5 mmoles of trimethylsilyl perchlorate $[(CH_3)_3Si—O—ClO_3]$ in 20 ml of benzene, and the whole was allowed to stand for 1 week at 24°C. After the addition of 50 ml of chloroform, the mixture was agitated with 50 ml of an ice-cold saturated solution of sodium bicarbonate, and separated, and the aqueous phase was then agitated with a small amount of chloroform. After drying with sodium sulphate and evaporation there were obtained 2.8 grams of crude product, which after recrystallization from 40 ml of benzene gave 2.1 grams (75.5% of the theoretical yield) of pure 2',3',5'-tri-O-benzyl-uridine melting at 138—140°C.

Example 2

The procedure was the same as that described in Example 1, except there was added only 0.5 mmole of trimethylsilyl perchlorate (in 5 ml of benzene) and boiling was carried out for 4 hours at a 100°C bath temperature under argon. After working up and crystallization there were obtained 2.238 grams (80.4% of the theoretical yield) of 2',3',5'-tri-O-benzyl-uridine.

Example 3

To 10 mmoles of 3-trimethylsilylthio-5-trimethylsilyloxy-1,2,4-triazine and 10 mmoles of β-glucose-penta-acetate in 25 ml of 1,2-dichlorethane was added 1 mmole of trimethylsilyl perchlorate in 7 ml of benzene, and the whole was boiled for 3

hours at a 100°C bath temperature. After the usual working up as described in Example 1 there were obtained 3.5 grams of crude product, from which there were obtained from ethanol 3 grams (65% of the theoretical yield) of 2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-thio-2,3,4,5-tetrahydro-1,2,4-triazin-5-one melting at 226°C.

Example 4

To 5 mmoles of 2-trimethylsilyloxy-pyridine and 5 mmoles of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in 25 ml of 1,2-dichlorethane was added 0.5 mmole of the trimethylsilyl ester of trifluoromethane sulphonic acid in 1 ml of benzene, and the whole was boiled for 1.5 hours at a 100°C bath temperature and worked up as described in Example 1. After crystallization of the resulting residue (2.8 grams) from 75 ml of carbon tetrachloride there were obtained 2.28 grams (85% of the theoretical yield) of 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,2-dihydro-pyridin-2-one melting at 140°C.

Example 5

To 10 mmoles of 2-O-trimethylsilyloxy-4-trimethylsilylamino-pyrimidine and 10 mmoles of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in 35 ml of 1,2-dichlorethane were added 12 mmoles of the trimethylsilyl ester of trifluoromethane sulphonic acid [$(CH_3)_3SiO—SO_2CF_3$] in 24 ml of benzene, and the whole was heated for 1 hour at 100°C. Working up as described in Example 1 gave 3.869 grams (85% of the theoretical yield) of amorphous 2',3',5'-tri-O-benzyl-cytidine.

Example 6

To 10 mmoles of 6-benzoyl-trimethylsilylamino-9-trimethylsilyl-purine and 10 mmoles of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in 35 ml of 1,2-dichlorethane was added 1 mmole of trimethylsilyl perchlorate in 7 ml of benzene. After 12 hours at a bath temperature of 100°C and working up as described in Example 1, there was obtained amorphous tetrabenzoyl-adenosine, which was hydrolysed with 250 ml of methanolic ammonia for 16 hours at 22°C. By evaporation and extraction with methylene chloride there were obtained from methanol-H_2O 2.3 grams (86.4% of the theoretical yield) of pure adenosine, melting at 230—232°C.

Example 7

To 40 mmoles of 2,4-bis-(trimethylsilyloxy)-lumazine and 40 mmoles of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in 75 ml of 1,2-dichlorethane were added 4 mmoles of trimethylsilyl perchlorate in 20 ml of benzene, and the whole was boiled for 4 hours at a bath temperature of 100°C. By working up as described in Example 1 there were obtained 20.2 grams (84% of the theoretical yield) of 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-lumazine.

Example 8

To 55 mmoles of 1-trimethylsilyl-3-carboxymethyl-1,2,4-triazole and 55 mmoles of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in 100 ml of 1,2-dichlorethane were added 5 mmoles of $(CH_3)_3SiO—SO_2CF_3$ in 20 ml of benzene, and the whole was boiled for 4 hours at a bath temperature of 100°C. By working up as described in Example 1 there were obtained 24 grams (85.5% of the theoretical yield) of 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-3-carboxymethyl-1,2,4-triazole.

Example 9

To 10 mmoles of 2,4-bis-(trimethylsilyloxy)-5-morpholino-pyrimidine and 10 mmoles of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in 35 ml of 1,2-dichlorethane were added 11 mmoles of $(CH_3)_3SiO—SO_2CF_3$ in 20 ml of benzene, and the whole was stirred for 20 hours at room temperature under argon. Working up as described in Example 1 yielded 6.36 grams (99% of the theoretical yield) of amorphous 5-morpholino-2',3',5'-tri-O-benzyl-uridine.

Example 10

11 mmoles of 2,4-bis-(trimethylsilyloxy)-5-methoxy-pyrimidine and 12 mmoles of $(CH_3)_3SiO—SO_2CF_3$ dissolved in absolute 1,2-dichlorethane were added to 5.04 grams (10 mmoles) of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in 75 ml of 1,2-dichlorethane, and the whole was stirred for 4 hours at room temperature. Working up as described in Example 1 yielded from ethyl acetate/hexane 5.24 grams (89.3% of the theoretical yield) of 5-methoxy-2',3',5'-tri-O-benzoyl-uridine.

Example 11

11 mmoles of 2,4-bis-(trimethylsilyloxy)-5,6-dimethyl-pyrimidine and 12 mmoles

of $(CH_3)_3SiO—SO_2CF_3$ dissolved in absolute 1,2-dichlorethane were added under argon to 5.04 grams (10 mmoles) of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in 75 ml of 1,2-dichlorethane, and the whole was stirred for 3.5 hours at room temperature. Working up as described in Example 1 yielded from methylene chloride/hexane 4.8 grams (82.2% of the theoretical yield) of 5,6-dimethyl-2′,3′,5′-tri-O-benzoyl-uridine.

Example 12

To a solution of 5.04 grams (10 mmoles) of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in 100 ml of absolute acetonitrile were added under argon 11 mmoles of 2,4-bis-(trimethylsilyloxy)-6-methyl-pyrimidine and 12 mmoles of $(CH_3)_3SiO—SO_2CF_3$ in absolute acetonitrile, and the whole was stirred for 3 hours at room temperature. Working up in accordance with Example 1 and column chromatography with ethyl acetate/hexane yielded from ethyl acetate/hexane 4.04 grams (70.9% of the theoretical yield) of 6-methyl-2′,3′,5′-tri-O-benzoyl-uridine.

Example 13

In a manner analogous to that described in Example 12 were reacted 5.04 grams (10 mmoles) of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose, 11 mmoles of 1-(trimethylsilyloxy)-1,2,4-triazole and 12 mmoles of $(CH_3)_3SiO—SO_2CF_3$. Working up as described in Example 1 yielded 2.94 grams (57.2% of the theoretical yield) of 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole melting at 105—106°C.

WHAT WE CLAIM IS:—

1. A process for the manufacture of a nucleoside, wherein a sugar derivative that contains an -O-acyl or -O-alkyl group or a halogen atom in the 1-position and may contain at least one protected hydroxyl group in another position is reacted with a silylated organic base in the presence of an ester selected from trialkylsilyl esters of mineral acids and trialkylsilyl esters of strong organic acids and, if desired, any protected hydroxyl group in the resulting nucleoside is converted into a free hydroxyl group.

2. A process as claimed in claim 1, wherein the reaction is carried out in the presence of an ester selected from trimethylsilyl esters of mineral acids and trimethylsilyl esters of strong organic acids.

3. A process as claimed in claim 2, wherein the ester is trimethylsilyl perchlorate.

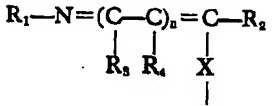
4. A process as claimed in claim 2, wherein the ester is the trimethylsilyl ester of trifluoromethane sulphonic acid.

5. A process as claimed in any one of claims 1 to 4, wherein in the sugar derivative all the hydroxyl groups are protected.

6. A process as claimed in any one of claims 1 to 5, wherein the sugar is ribose, desoxyribose, arabinose or glucose.

7. A process as claimed in any one of claims 1 to 6, wherein the silylated organic base is a silylated heterocyclic organic base.

8. A process as claimed in any one of claims 1 to 6, wherein the silylated organic base is a compound of the general formula



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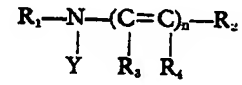
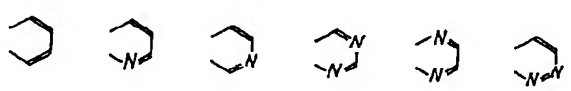
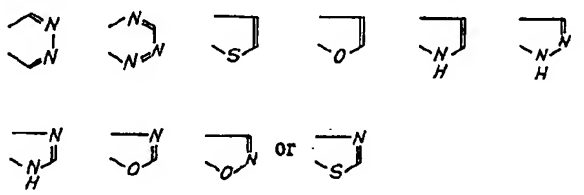


(Ib)

in which n represents 0 or 1, X represents an oxygen or sulphur atom, R_1 and R_2 each represents an unsubstituted or substituted organic hydrocarbon group or together represent a divalent organic group, R_3 and R_4 each represents a hydrogen atom or an alkyl, alkoxycarbonyl or alkylaminocarbonyl group or together represent either a divalent group of the formula

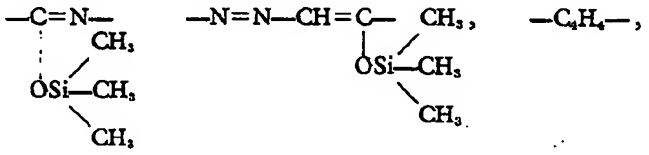


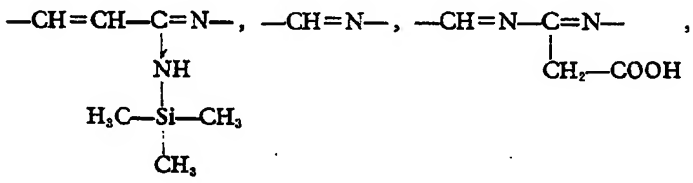


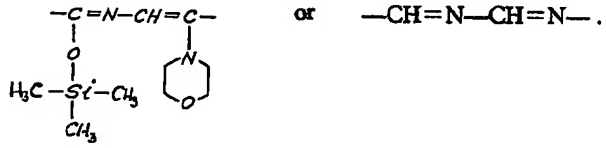
or a corresponding divalent group that is substituted, and Y represents a trialkylsilyl group.

9. A process as claimed in claim 8, wherein the divalent organic group represented by R_1 and R_2 together contains 1 or 2 nitrogen atoms.

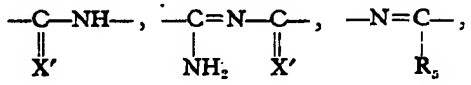
10. A process as claimed in claim 8, wherein the divalent organic group represented by R_1 and R_2 together is a group of the formula

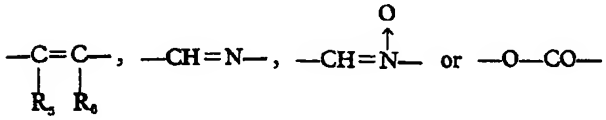






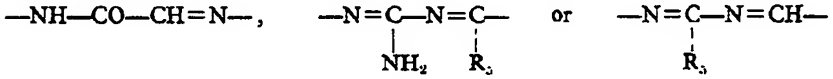
11. A process as claimed in claim 8, wherein n represents 1 and R_1 and R_2 together represent a





group in which X' represents an oxygen or sulphur atom and R_5 and R_6 each represents a hydrogen atom or an alkyl, alkoxycarbonyl or alkylaminocarbonyl group.

12. A process as claimed in claim 8, wherein n represents 0 and R_1 and R_2 together represent a



group in which R_5 represents a hydrogen atom or an alkyl, alkoxycarbonyl or alkylaminocarbonyl group.

13. A process as claimed in any one of claims 8 to 12, wherein Y represents a trimethylsilyl group.

14. A process as claimed in any one of claims 1 to 13, wherein the reaction is carried out at a temperature within the range of from 0 to 100°C.

15. A process as claimed in claim 1, conducted substantially as described herein.

16. A process as claimed in claim 1, conducted substantially as described in any one of Examples 1 to 8 herein.

17. A process as claimed in claim 1, conducted substantially as described in any one of Examples 9 to 13 herein.

18. A nucleoside whenever made by the process claimed in any one of claims 1 to 17.

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